Uric Acid and Cardiovascular Disease: An Update

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Abstract

In recent years, serum uric acid (SUA) as a determinant of cardiovascular (CV) risk has gained interest. Epidemiological, experimental and clinical data show that patients with hyperuricaemia SUA are at increased risk of cardiac, renal and vascular damage and CV events. There is now some evidence to suggest that urate-lowering treatment may reduce CV risk in this group and, thus, may represent a new strategy in risk reduction.

Keywords

Uric acid, CV disease, xanthine-oxidase inhibitors, AF, heart failure, target organ damage

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Uric acid (UA) represents the final product of purine metabolism, in humans mainly regulated by the xanthine-oxidoreductase enzyme, which converts hyoxantine to xanthine and xanthine to UA. Dietary factors may influence serum UA (SUA), increasing its levels (meat, seafood, fructose, alcohol and sodium) or decreasing them (coffee and ascorbic acid). In addition, high cellular turnover conditions, i.e. in neoplastic diseases, may increase UA concentration.

UA may have an opposite role to oxidative stress, according to its intracellular (anti-oxidant) and extracellular (pro-oxidant) localisation.[1] The xanthine-oxidoreductase enzyme isoform xanthine-oxidase (XO) generates reactive oxygen species (ROS) as byproducts and may have a detrimental effect on vascular endothelium. The production of ROS induced by UA seems paradoxical since UA is considered to be one of the anti-oxidants that protects the cardiovascular (CV) system from stress. UA prevents the protein nitrosylation induced by peroxynitrite, the peroxidation of lipids and proteins and the inactivation of tetrahydrobiopterin, which results in scavenging free radicals and chelating transitional metal ions.[2] UA administration in healthy volunteers and athletes reduced ROS production,[3] confirming its intrinsic anti-oxidant activity.

Experimental and human studies have demonstrated the role of UA as a pro-oxidant, inducing endothelial dysfunction. This may be improved by the administration of XO inhibitors, while other urate-lowering drugs (ULDs) acting through an uricosuric action are ineffective.[4] The increase in oxidative stress resulting from the increased activity of XO could also explain the link between elevated UA and hypertension, as observed in animal models. In rats, the administration of oxonic acid, an inhibitor of uricase, may induce hyperuricaemia and a proportional increase in blood pressure (BP).[5]

UA may also stimulate the renin–angiotensin system (RAS), further contributing to vascular smooth cell growth, and arterial function impairment and stiffening. The possible role of systemic inflammation – measured by markers such as C-reactive protein (CRP), tumour necrosis factor or chemokine associated with hyperuricaemia – has also been explored, showing a further contribution to CV damage.[6]

The role of SUA in the development of arterial hypertension (AH) was highlighted in 1879 and 10 years later Haig[7] proposed a low-purine diet as a means to prevent hypertension and CV diseases (CVDs). In 1909, Huchard described the association between renal arteriosclerosis and chronic hyperuricaemia.[8]

Since 1960, a number of epidemiological studies have found an association between SUA levels and different CV risk factors or diseases, such as AH, ischaemic stroke and acute and chronic heart failure (HF). The correlation is clearly present at SUA levels of 5–5.5 mg/dl,[9] a range that is lower than the <6 mg/dl suggested by the European League Against Rheumatism[10] and the American College of Rheumatology.[11]

The lack of a clear causal mechanism explaining the association between hyperuricaemia and CV risk factors and disease has led to the relevance of SUA being ignored.[12] The results of the Framingham study, comprising 6,763 subjects followed for about 20 years, did not confirm an increase in the risk of CV death and SUA in men, but did in women.[13] However, the increased risk lost statistical significance after taking into account confounders. On the contrary, Abbott et al.[14] described in the same population a significant increase in coronary artery disease (CAD) in men with chronic hyperuricaemia and crystal deposits.

A systematic review has confirmed that chronic hyperuricaemia with crystals deposit is strictly related to an increased risk of CV and all-cause death.[15]

The exact role of SUA as a marker or cause of CVD has been extensively discussed.[16] In most of the published studies, SUA concentrations are related to age, sex, degree of kidney function, BP levels and metabolic abnormalities.

An independent relationship between UA and CV events has been frequently observed and a causal role of SUA has been proposed. The evidence that BP values may improve by treatment that lowers SUA seems to support a possible causal link between SUA and CVD.[17,18]

Hyperuricaemia and Target Organ Damage

The association between elevated SUA and CV risk factors, all contributing to the development of vascular, cardiac and renal target organ damage, has been extensively evaluated, with some controversial results.

Some studies have reported that elevated SUA is strongly associated with coronary[19] and carotid[20,21] atherosclerosis, especially in women. The Atherosclerosis Risk in Communities (ARIC) study[22] observed that the SUA level was significantly associated with B-mode ultrasound carotid intima-media thickness (considered an early measure of atherosclerosis). Subsequently, Mutluay et al. reported that hyperuricaemia is an independent predictor of early atherosclerosis in hypertensive subjects with normal renal function.[23] Similar results were obtained by Cicero et al. in an Italian epidemiological study evaluating 248 men and 371 women adult individuals not consuming anti-hypertensive, anti-diabetic, lipid- or UA-lowering drugs.[24] These results suggest that SUA may have an atherogenic role in the pathophysiology of CVDs; however, the precise mechanisms have not been fully elucidated. Experimental studies have shown that UA may stimulate vascular smooth muscle cell proliferation *in vitro*, with the production of pro-inflammatory and pro-oxidative and vasoconstrictive substances.[25,26] Moreover humans' atherosclerotic plaque may contain a considerable amount of UA,[27] which may increase platelet adhesion and thrombus formation.[28] On the other hand, some studies also show a role for XO, which is responsible for oxidative processes[29] and endothelial dysfunction, thus independendtly affecting the occurrence of CVDs.

Hypertensive patients with left ventricular hypertrophy (LVH) have higher SUA levels, independent of other CV risk factors, and a more strict association between SUA and LV mass index was observed in women.[30–34] When 24-hour BP values were taken into account, a Japanese study confirmed this association.[33] In some of these studies the association was more evident in women than in men[33] or vice versa.[32]

More recently, in uncomplicated patients without chronic kidney disease (CKD), and with a recent diagnosis of hypertension[34] or at low CV risk,[35] the correlation between SUA and LV mass did not reach statistical significance when all the potential confounders, including 24-hour BP, were taken into account.

Iwashima et al.[36] also observed that hyperuricaemia and LVH were independent predictors of CV events (acute MI, angina, HF, stroke or transient ischaemic attack), but the combination of LVH and hyperuricaemia was associated with a further increase in the incidence of CV events.

Several mechanisms may explain the increase in LV mass in the presence of hyperuricaemia, including the systemic inflammatory response, RAS activity,[37] endothelial dysfunction[38] or the expression of endothelin-1 in cardiac fibroblasts, thus favouring cardiac interstitial fibrosis.[39] In addition, some indirect effects of hyperuricaemia, such as increased BP, the parallel decrease of glomerular filtration rate (GFR), the impairment of platelet adhesion and aggregation and the increase in aortic stiffness, could further contribute to the development of LVH. Vlachopoulos et al.[40] observed a close relationship between carotid–femoral pulse wave velocity and SUA in a large cohort of never-treated hypertensive patients, mainly in women; an increase in large artery stiffness and arterial wave reflections are important determinants of LV mass and function and coronary blood flow.

In the Framingham Offspring cohort (n=2,169, mean age 57 years, 55 % women) a decrease in systolic function parameters was observed in subjects with SUA >6.2 mg/dl compared with those with lower.[41] These results, showing an early impairment of LV function in the presence of a modest increase in SUA could, in part, explain the association between elevated SUA and the increased risk of incident HF and poor outcomes in HF patients with elevated SUA, as recently confirmed in a meta-analysis[42] and suggested by the Framingham Offspring study.[43] A more severe impairment of diastolic function has been observed in hypertensive patients with hyperuricaemia.[33]

Few data are available on the effect of changes in SUA induced by diet modification or pharmacological treatment. In the Losartan Intervention For Endpoint reduction in Hypertension study (LIFE), patients with electrocardiographic signs of LVH were randomised to losartan or atenolol: a greater decrease in LVH was associated with a less marked increase in SUA level during therapy with losartan compared with atenolol.[44]

The effect of allopurinol and febuxostat were compared in a small number of patients with gout. A more favourable effect of febuxostat on both carotid–femoral pulse wave velocity and oxidative stress was found.[45]

Only one study has examined the effect of UA-lowering treatment on target organ damage in patients with CKD,[46] which showed a decrease of LV mass (evaluated by nuclear magnetic resonance), and an improvement of flow-mediated vasodilation and of augmentation index after allopurinol treatment compared with placebo.

SUA level has also emerged as a risk factor for the development and progression of CKD. Afferent arteriolar thickening and ischaemic renal changes, associated with an increase in systemic BP and renal glomerular pressure, have been described in rats with hyperuricaemia induced by oxonic acid or a high-fructose diet; all these changes may be prevented by lowering SUA with XO inhibitors.[47–49] Furthermore, epidemiological studies have reported that asymptomatic hyperuricaemia is strongly associated with both CKD and end-stage kidney disease;[50–52] however, hyperuricaemia may represent a consequence of reduced renal excretion in patients with CKD and therefore be a marker of kidney function. A recent review and meta-analysis has shown that SUA-lowering therapy with allopurinol may slow the progression of CKD. Further adequately powered randomised trials are required to evaluate the benefits and risks of SUA-lowering therapy in CKD.[53]

Hyperuricaemia and Cardiovascular Disease

In the past 50 years, the results of several studies have assessed and promoted the role of UA as an independent risk factor for CV and renal diseases. In this regard, strong evidence comes from the first National Health and Nutrition Examination Survey (NHANES I), performed in the US between 1971 and 1975 in a general population sample of 20,729 individuals aged 25–74 years. In the National Health Epidemiologic Follow-up Study (NHEFS), all participants in the NHANES

I were prospectively followed, and the all-cause, CV and CAD deaths were assessed; in a subgroup of 6,912 subjects data were analysed according to SUA level.[54] The results showed a significant positive association between increasing levels of SUA and CV (including CAD) mortality, independent of other traditional risk factors, in both men and women, confirming previous data obtained after a shorter follow-up of the NHANES I population.[55] In the previous study[55] elevated SUA level was an independent predictor of all-cause and ischaemic heart disease mortality for women only and 1 mg/dl increase of SUA was associated with a 48 % increase in the risk of CAD.[55]

In a prospective study conducted in Rotterdam, 4,385 men and women >55 years of age without history of stroke or coronary heart disease, an association between baseline SUA levels and risk of both MI and stroke was confirmed.[56] In a further analysis, a U-shape relationship between SUA and both all-cause and CV mortality was shown, indicating that both low and high SUA levels were prognostically deleterious.[57]

A further demonstration of the association between SUA and CV risk is given by the results of the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study, in which individuals aged 25–74 years were examined and followed-up for up to 16 years.[58] For 2,045 subjects a baseline SUA was available: a mean value of 4.9±1.3 mg/dl was observed with significantly higher values in men with respect to women. During follow-up, 342 subjects died, (32 % from CV causes). Mean SUA (5.54 mg/dl) observed in patients who died was higher when compared with those who survived (4.82 mg/dl); a significant difference in mean SUA level was observed between patients who died of CV causes (5.74 mg/dl) or (4.89 mg/dl).[59] A significant increase of the risk of CV death for every 1 mg/dl increase of SUA was observed, while the same was not true for all-cause death after adjustment for confounders.

The effect of elevated SUA levels on the incidence of CADs seems to be stronger in women than in men, as shown by an epidemiological study conducted in the US, which originally enrolled 3,102 subjects between 1960 and 1962, with a follow-up of 7 to 9 years. In 2,530 subjects attending the second examination, SUA was measured and urate concentrations were about 1 mg/dl higher in men than in women in the younger decades of age, while in women a consistent increase in SUA was observed after physiological menopause;[60] race did not protect significant differences.

Other studies have analysed the association between SUA and CV risk in hypertensive and/or patients with diabetes.

In the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, which examined 1,720 untreated hypertensive patients enrolled between 1986 and 1996,[61] the highest SUA levels (>6.2 mg/dl in men; >4.6 mg/dl in women) were significant predictors of all-cause deaths and of CV events, again independently of traditional confounders, including LVH. Also in this study, a J-shaped curve relationship between SUA levels and CV events was observed, with the lowest risk occurring at UA concentrations of 4.5–5.2 mg/dl in men and 3.2–3.9 mg/dl in women.

Almost 8,000 patients with mild to moderate hypertension living in New York, USA were studied by Alderman et al. from 1973 to 1996, showing that baseline SUA levels were associated with the subsequent occurrence of CV events; more precisely, the in-treatment SUA levels were predictive of a worse CV prognosis, independently of creatinine, diuretic treatment, race and all traditional CV risk factors.[62]

The LIFE study presented data from 9,193 hypertensive patients with electrocardiographic LVH, and showed a greater efficacy of a losartan-based therapeutic regimen compared with atenolol in the regression of LVH and in the prevention of fatal and non-fatal CV events (acute MI, stroke and CV deaths). At study end, UA levels were lower in patients treated with losartan than with atenolol, with a relative risk reduction of 29 % for CV events. This difference reached statistical significance in women, but not in men, after adjustment for all traditional risk factors and confounders,[44] supporting again the evidence that hyperuricaemia may confer a less favourable CV prognosis in women rather than in men.

In the observational study Blood Pressure control rate and CV Risk profilE (BP-CARE), in which 7,800 treated hypertensive patients from Central and Eastern Europe were included,[63] the CV risk profile was positively and significantly related to SUA levels and to the presence of urate deposits (gout).

When examining the population with diabetes, similar results have been obtained. In 1993, Rathmann et al. reported a positive correlation between SUA and CAD in women with type 1 or 2 diabetes.[64] In a prospective study including 1,017 men and women (aged 45–64 at baseline) patients with type 2 diabetes were followed up for 7 years;[65] 31 patients died from stroke and 114 patients had a fatal or non-fatal stroke. High SUA levels were associated with the risk of fatal and non-fatal stroke (hazard ratio [HR] 1.93; CI 95 % [1.30–2.86]; P<0.001) and stroke incidence increased significantly by SUA quartiles.

In patients with diabetes, the correlation between SUA and CV function has been attributed to the same mechanisms that lead to renal dysfunction, including activation of the renin-angiotensin-aldosterone system (RAAS) and ROS pathways, nitric oxide (NO) synthase inhibition, autonomic dysfunction and increase in BP.[49,66,67]

A large meta-analysis published in 2013, evaluating only prospective studies on CV or all-cause mortality related to SUA confirmed that baseline SUA is an independent predictor of future CV mortality. Elevated SUA appears to significantly increase the risk of all-cause mortality in men, but not women. No conclusive data on whether low SUA predicts mortality were shown.[68]

Most of the differences and limitations of currently available published studies are the limited number of individuals included and the inclusion criteria. Urate deposits are difficult to evaluate and therefore we do not know whether individuals included in the studies have urate deposits or not.

Despite epidemiological data showing lower mean SUA in women, some studies report that an increase in SUA has a detrimental effect on CV health in women[30,55] and one meta-analysis has shown a significant relationship between an increase in SUA and coronary events in women but not in men.[69] The mechanisms that underlie the unfavourable influence of SUA on major CV events in women remain uncertain and whether different cut-off vales according to sex are needed should be assessed in future studies.

Hyperuricaemia and Atrial Fibrillation

Oxidative stress may influence the development of AF, in addition to neurohormonal and inflammatory activation. Both inflammation and

neurohormones may activate XO and increase SUA. In experimental studies, oxidative stress has been shown to induce atrial electric remodelling, thus favouring the re-entry mechanism[70] as well as NO decrease, shortening of action potential plateau duration, increase of the repolarisation velocity and AF.[71,72] The relationship between the increase in oxidative stress markers and AF has been observed in patients with valvular diseases or after coronary bypass surgery; after radiofrequency ablation AF recurrence was higher in patients with the higher levels of oxidative stress markers.[73] In addition, it is reasonable that other risk factors (RAAS hyperactivity), vascular abnormalities (endothelial dysfunction) or LVH associated with UA increase may further promote the development of AF.

A case-control study examining Greek patients with AF was among the first to suggest an association between SUA and AF.[74] In the ARIC study, which included 15,382 subjects aged 45–64 years, the incidence of AF paralleled the increase in SUA concentration, and the relationship remained significant after taking into account all the possible confounders, including diuretic treatment and P-wave duration (index of left atrial enlargement). In this study the increase of 1 standard deviation of SUA was associated with a 16 % increase in AF risk, mainly among African Americans and women.[75] The rate of hyperuricaemia observed in African Americans could be ascribed to genetic differences, since African Americans have a higher prevalence of the gene *SLC2A9*, favouring SUA reabsorption in the proximal renal tubule.[75] The data have been further confirmed in patients with paroxysmal or permanent AF.[76]

A recent meta-analysis[77] that evaluated six cross-sectional studies (n=7,930) and three cohort studies (n=138,306 subjects without AF) confirmed an increase in the relative risk of AF among those with high SUA (relative risk = 1.67 (95 % CI [1.23–2.27]) compared with those with normal SUA.

Hyperuricaemia and Heart Failure

In the Cardiovascular Health Study, the incidence of HF was 21 % in participants with chronic hyperuricaemia and 18 % in those without; the results showed that an increase of 1 mg/dl in SUA conferred a 12 % increase in risk of new HF.[78] In the Framingham Offspring study the incidence of HF was sixfold higher among individuals with SUA levels in the higher quartile (>6.3 mg/dl) than those with levels in the lowest quartile (<3.4 mg/dl).[79–81]

Chronic hyperuricaemia is a frequent finding in patients with HF, with a prevalence >50 % in hospitalised patients with chronic HF.[82] The severity of hyperuricaemia is related to New York Heart Association (NYHA) functional class, to higher maximal oxygen consumption and to the degree of diastolic dysfunction impairment. The highest UA concentrations may be observed in patients with advanced chronic HF or cardiac cachessia.

In the Derivation study, SUA was the strongest prognostic variable in patients with severe chronic HF (NYHA class III or IV):[78,79] in patients with chronic hyperuricaemia (SUA >9.5 mg/dl) the relative risk of death was 7.4.

In patients with acute and chronic HF, SUA concentration represents a prognostic marker of all-cause mortality independent of traditional prognostic determinants, as shown by Tamaris et al.[81]

A more recent meta-analysis addressing the association between SUA and incidents HF and/or the prognosis of HF patients, was performed by Huang et al.[42] Five studies reporting on incident HF and 28 studies reporting on HF outcomes were included. The results showed that hyperuricaemia was associated with an increased risk of incident HF (HR 1.65; 95 % CI [1.41–1.94]). In addition, for every 1 mg/dl increase in SUA the risk of all-cause mortality and the composite endpoint in HF increased by 4 % and 28 %, respectively. Subgroup analyses supported the positive association between SUA and HF.

A retrospective case-control-led analysis of patients with symptomatic HF showed that hyperuricaemia was significantly associated with increased events (HF hospital readmission or all-cause mortality).[42] In this study the use of allopurinol was associated with a reduction in events (adjusted relative risk 0.69; 95 % CI [0.60–0.79]).[82] In the Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) study, 1,600 patients with CAD were followed for 3 years, and a reduction in SUA concentrations, possibly induced by the use of atorvastatin, was associated with a lower incidence of CV events, including coronary events.[83]

SUA plays a role in HF incidence and development that is not still completely understood. The impairment in GFR, even to a mild degree, causes a decrease in renal UA excretion.[84–86] The increase in lactate concentration, and the hyperactivity of the sympathetic nervous system and the RAASs, may further contribute to SUA increases by increasing UA reabsorption. Finally, in patients with HF, the use of diuretics may induce a further reduction in UA excretion.[87]

According to another pathogenetic hypothesis, SUA functionally up-regulates XO, which is a key enzyme in purine metabolism. XO-derived ROS may account for a range of detrimental processes in the pathophysiology of HF, such as cardiac hypertrophy, myocardial fibrosis, LV remodelling and contractility impairment. In addition, UA *per se* may represent a 'proinflammatory' substance, frequently associated with other inflammatory markers such as CRP, interleukin-6 and neutrophil leukocytes. In fact, in a large group of older patients, affected by mild-to-moderate hypertensive and/or ischaemic HF, SUA was inversely related with ejection fraction (EF); the predicted role of SUA was apparently independent of filtration rate and use of diuretics.[88]

In the Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in Patients With New York Heart Association Class III–IV Congestive HF (OPT-CHF), which enrolled 405 patients with systolic HF (EF >40 %), randomised to treatment with allopurinol or placebo, on top of standard therapy, the use of the XO inhibitor was associated with an increase in EF and to a clinical improvement among patients with elevated SUA.[89] Thus, XO inhibition may be associated with an improvement in haemodynamics and clinical outcomes in hyperuricaemic patients.[89,90] Conversley, this was not observed when the UA concentration was obtained by treatment with an uricosuric drug (benzbromarone)[91] or oxypurinol.[92]

The US Food and Drug Administration approved a non-purine XO inhibitor, febuxostat, for the treatment of gout. Experimental data have shown that febuxostat may reduce the development of LVH and the amount of cardiac collagen content, thus improving systolic function.[93] In a small study, 141 cardiac surgery patients with CKD were randomised to treatment with allopurinol or febuxostat: superior anti-oxidant and anti-inflammatory effects and a more favourable change in renal dysfunction were observed during treatment with febuxostat than with allopurinol.[94]

New data are needed to establish the clinical benefit of treatment with different XO inhibitors in patients with hyperuricaemia, with and without UA deposits, and HF.

Conclusion

From the available epidemiological data it is clear that hyperuricaemia is associated with a greater risk of target organ damage and of CV morbidity and mortality.

The increase in risk is stronger in patients at high CV risk and in patients with SUA levels >6 mg/dl. Deleterious effects are substantially independent of the presence of urate crystals in the joints.

No strong evidence is available to show that lowering SUA is associated with a decreased incidence of CV events in patients without gout; the use of ULDs is not approved in patients with asymptomatic hyperuricaemia. Large controlled trials are ongoing to assess the effect of SUA-lowering drugs on CV events.[95] ■

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